Syntheses of Lactones related to Psilostachyins

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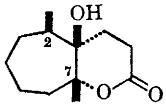
RECENTLY a new class of dilactones[1] known as psilostachyin along with psilostachyin (B) and (C) has been isolated. These are evidently formed through oxidative opening[2] of the five-membered ring present in pseudoguaianolides. To achieve a total synthesis of this type of natural products, we have synthesised the lactones (I) and (II) as model compounds.

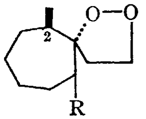
The condensation product from ethyl 6-bromohexanoate[3] and diethyl methylmalonate on hydrolysis and subsequent esterification afforded diethyl α-methylsuberate. This was subjected to Dieckmann cyclisation with potassium t-butoxide suspended in boiling xylene according to high dilution technique.[4] The cyclised product underwent condensation *in situ* with methyl iodide to give 2-ethoxycarbonyl-2,7-dimethylcycloheptanone in an excellent yield, which on acidic hydrolysis gave 2,7-dimethylcycloheptanone in a good yield (orange 2,4-dinitrophenylhydrazone, m.p. 99°). The ketone was found by g.l.c. analysis to be a mixture of two components in the proportion (82 : 16) together with minor constituents (*ca.* 2%). It has two methyl groups situated alpha to the carbonyl group and these are capable of being epimerised. Therefore the component present to the extent of 82% may be *cis*-2,7-dimethylcycloheptanone. This is supported by the formation of the keto-lactone (III) in a good yield from 2-ethoxycarbonyl-2,7-dimethylcycloheptanone through the corresponding α-bromoketone. The other component (16%) may be the *trans*-2,7-dimethylcycloheptanone. The following experiments confirm these stereochemical assignments.

The ketone(s) were treated with allylmagnesium bromide[5] to give the unsaturated alcohol(s) (IV) in an excellent yield. Diborane[6] was bubbled through the unsaturated alcohol(s) in tetrahydrofuran and the crude residue was oxidised with chromic acid[7] to yield the spirolactone(s) (V), ν_{max} ($CHCl_3$) 1755 cm.$^{-1}$. Gas–liquid chromatography showed it to be a mixture of two components (80 : 16) together with minor constituents (*ca.* 4%). Hydroboration of the unsaturated alcohol(s) (IV), followed by treatment with alkaline hydrogen peroxide,[8] furnished the diol(s) (VIa). Oxidation of the diol(s) afforded the same mixture of spiro-lactone(s) (V) as shown by g.l.c. analysis.

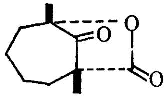
The diols (VIa) were treated under reflux with acetic anhydride in the presence of freshly fused sodium acetate to give the unsaturated acetate (VII). The n.m.r. spectra† of the unsaturated acetate suggest the structure (VIIa): 1·04 p.p.m. (d, J = 7·2 c./sec., 2- and 7-Me), 2·0 (s, CH_3·CO),



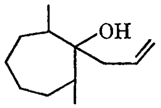
(I)



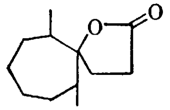
(II) R=—Me
(XII) R=···Me



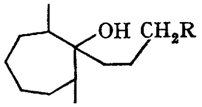
(III)



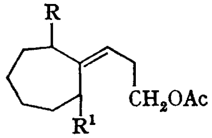
(IV)



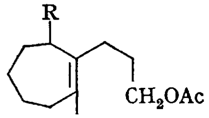
(V)



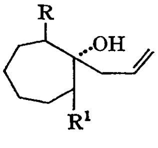
(VIa) R=OH
(VIb) R=OAc



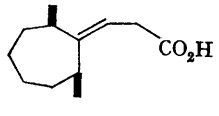
(VIIa) R=R^1=Me
(X) R=R^1=—Me



(VIIb) R=Me
(XI) R=—Me



(VIII) R=R^1=—Me
(IX) R=—Me, R^1=····Me



(XIII)

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† The n.m.r. spectra measured on a Varian A60 instrument; results quoted in p.p.m. with respect to Me_4Si used as an internal standard.

5·2 (t, J = 7·2 c./sec., CH=), and 4·00 (t, J = 6·6 c./sec., OCH_2). The presence of a low intensity singlet at 1·28 p.p.m. can be assigned to a tertiary methyl group, thereby suggesting that the isomeric acetate (VIIb) is also present in a lesser amount. G.l.c. analysis of the unsaturated acetate(s) (VII) also showed a mixture of two components in the proportion (80:15) together with minor constituents (*ca.* 5%). The same proportions were obtained when the mono-acetate (VIb) was dehydrated with phosphorus oxychloride in pyridine. Mode of dehydration suggests that the unsaturated alcohol(s) (IV) should have stereochemistry as depicted in (VIII) and (IX), and the corresponding unsaturated acetates may be represented as (X; 80%) and (XI; 15%) respectively. The spirolactone present to the extent of 80% may be assigned the stereochemistry as shown in (II) and the other lactone present in a lesser amount (15%) may be depicted as (XII), because its formation from (VIII) and (IX) involves no inversion.

The unsaturated acetate(s) (VII) was saponified to give the corresponding unsaturated alcohol(s), which on oxidation with Jones reagent[7] furnished the related unsaturated acid(s). Its methyl ester(s) was treated with an excess of monoperphthalic acid in ether at 0°, and the crude epoxide formed was boiled with NaOH (5%) to effect ring opening of the epoxide in a *trans*-fashion. The products were separated into neutral and acidic fractions present in the proportion (17:83). The neutral fraction solidified on chromatography, m.p. 68°, and corresponded to the hydroxy-lactone (I); ν_{max} ($CHCl_3$) 3620 and 1725 cm.$^{-1}$. The structure (I) was further confirmed from its n.m.r. spectra:† 1·04 p.p.m. (d, J = 7·0 c./sec., 2-Me) 1·34 (s, 7-Me), and 2·0 (s, exchangeable, 1-OH). The diaxial opening of the epoxide would give rise to *cis*-δ-lactone. The methyl group at C-2 is in the equatorial position and should be β-oriented. Therefore the hydroxy-lactone may be given the stereochemical assignment as depicted in (I).

The acidic fraction (83%) was found to be (XIII); ν_{max} ($CHCl_3$) 1715 cm.$^{-1}$. In the n.m.r. spectra, it has one olefinic proton at 5·45 p.p.m. coupled to two protons at 3·15 p.p.m. (J = 7·5 c./sec.). Decoupling experiments confirmed this. Also there is a hydroxyl proton at 11·47 p.p.m. which suggests a carboxylic acid function. Further, both the methyl groups are split into doublets at 0·94 and 1·04 p.p.m. (J = 7·5 c./sec.). The acid is represented by the stereoformula (XIV). It is interesting to note that the βγ-unsaturated acid (XIII) resisted epoxidation with monoperphthalic acid under these conditions.

We thank Prof. D. H. R. Barton, F.R.S., Prof. Alex Nickon for n.m.r. spectra, Dr. Sukh Dev for n.m.r. spectra and v.p. chromatography, and Prof. M. V. George of I.I.T., Kanpur, for i.r. spectra. We acknowledge financial assistance from the Chemical Society Fund. One of us (O.S.B.) thanks the C.S.I.R. for a senior fellowship.

(*Received, October 9th*, 1967; *Com.* 1083.)

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